

Applicants pointed out previously, and the Examiner does not dispute, that neither Morales nor Loria teach or suggest anything about the DHEA form(s) present in the preparations disclosed in these references. However, the Examiner notes:

Chang et al. teaches solid state crystallization of DHEA and its polymorph (forms I-III). Furthermore, it discloses that form I is more stable than others.

Office Action, page 3.

Applicants respectfully point out that the claimed invention relates to compositions having *at least 85%* form I DHEA. So the proper focus of the obviousness inquiry is whether Chang teaches or suggests compositions having this high a concentration of form I. Moreover, the Examiner must also consider whether Chang teaches or suggests compositions having 90%, 95%, and 99% form I DHEA, as recited in dependent claims 2 and 6 (90%); 3, 7, 37, and 39 (95%); and 4 and 8 (99%).

* * *

Applicants submit that Chang does not teach or suggest DHEA preparations that are at least 85% form I, much less how to achieve such preparations.

In particular, Chang fails to present any convincing evidence that such a preparation was prepared. Chang discloses form I-containing preparations, but merely assumes that these preparations were pure (see Chang, page 1173, col. 2). As Applicants' specification points out, this assumption was incorrect. Chang was unaware of the likelihood that their form I preparation was contaminated with a heretofore unknown form, namely form VI. In particular, note the passage at page 5, lines 7-20 of Applicants' specification, which explains that Chang's supposedly pure form I was actually a mixture of form I and form VI.

December 16 2002 Amendment, pages 4-6. The December 16 Amendment further stated:

Applicants respectfully submit that Chang provides no credible basis for the contention that one skilled in the art, following Chang, could produce such preparations. To the contrary, Applicants found that form I DHEA preparations can be contaminated with significant levels of form VI DHEA and that Chang's studies could not distinguish between DHEA preparations containing significant amounts (*i.e.*, greater than 15%) of form VI mixed with form I and substantially pure (*i.e.*, 85% or greater) form I preparations.

December 16 2002 Amendment, pages 6-7. In support of these statements, Applicants submit the Declaration of Dr. Patrick Stahly, the Chief Operating Officer and Vice President of Research and Development for SSCI, Inc. SSCI is a contract research laboratory specializing in crystallization, characterization, and chemistry of solids, and Dr. Stahly is an expert in the field of crystallization and polymorphism, as evidenced by his Curriculum Vitae (a copy of which is attached).

Dr. Stahly was asked to comment on whether a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would interpret Chang as describing dehydroepiandrosterone (DHEA) preparations containing at least 85% form I DHEA. Dr. Stahly's conclusion, based on actual experimental data, which accompany the declaration, is that a person of ordinary skill in this field would not view Chang as describing such preparations. Stahly Declaration, para. 10. In arriving at this conclusion, Dr. Stahly makes the following points:

1. "[S]tandard crystallization of DHEA out of organic solutions, such as Chang described, can yield mixtures of form I DHEA with significant amounts (*e.g.*, 30-40%) of form VI DHEA." Stahly Declaration, para. 4.
2. "None of the analytical techniques used by Chang to characterize the DHEA polymorph preparations can distinguish between form I DHEA and form VI DHEA." Stahly Declaration, para. 5. In support of this point, Dr. Stahly notes that Chang erroneously believed that X-ray powder diffraction could be used to estimate the purity of DHEA polymorphs. *Id.* at para. 6. However, Dr. Stahly demonstrates that "a mixture of form I and form VI DHEA exhibit essentially the same X-ray powder diffraction pattern as a pure form I preparation." *Id.* at para. 8.
3. "As described in the present application, solid state, carbon-13 NMR, a technique that Chang did not use, can distinguish between a pure form I DHEA preparation, a mixture of forms I and VI, and a pure form VI DHEA preparation." Stahly Declaration, para. 9. Using this technique, Dr. Stahly analyzed the form I:VI mixture and pure form I preparations which were indistinguishable by X-ray powder diffraction. *Id.* The results indicate that the form I:VI mixture contains on the order of 30-40% form VI DHEA (*i.e.*, at most, 60-70% form I DHEA), which was undetectable using X-ray diffraction. *Id.* at para. 10.
4. Thus, the results "establish that Chang's form I preparations could have contained as much as 40% form VI." Stahly Declaration, para. 10.

Dr. Stahly's Declaration establishes that Chang's purity estimates are not scientifically credible because of the likelihood that Chang's preparations were contaminated with a significant amount of form VI DHEA. Therefore, Chang, taken alone or with the other cited references, fails to teach or suggest preparations having 85% form I DHEA. Chang provides no motivation to remove form VI DHEA from form I DHEA to yield high-purity form I preparations because, as evidenced by Dr. Stahly's Declaration, Chang was unaware of the existence of form VI. Chang therefore necessarily fails to provide a reasonable expectation that such high-purity form I DHEA preparations could be achieved. Because none of the elements of a *prima facie* case have been met, Applicants respectfully request withdrawal of the § 103 rejection.

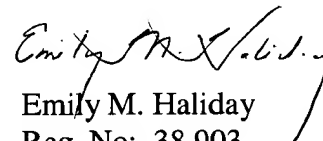
Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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Respectfully submitted,


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